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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :  A61K 9/127		A1	(11) International Publication Number: <b>WO 99/60999</b>  (43) International Publication Date: 2 December 1999 (02.12.99)
<p>(21) International Application Number: PCT/EP99/03681</p> <p>(22) International Filing Date: 27 May 1999 (27.05.99)</p> <p>(30) Priority Data: 60/086,895 27 May 1998 (27.05.98) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): EUROCELTIQUE S.A. [LU/LU]; Boulevard de la Petrusse 122, L-Luxembourg (LU).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): FLEISCHER, Wolfgang [DE/DE]; Posener Strasse 6, D-55218 Ingelheim (DE). REIMER, Karen [DE/DE]; Im Rehwinkel 12, D-65582 Hambach (DE).</p> <p>(74) Agent: MAIWALD, Walter; Maiwald GmbH, Elisenhof, Elisenstrasse 3, D-80335 München (DE).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PREPARATIONS FOR THE APPLICATION OF ANTI-INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE LOWER RESPIRATORY TRACT</p> <p>(57) Abstract</p> <p>Use of an anti-inflammatory agent such as povidone iodine for the preparation of a pharmaceutical composition for the treatment of diseases of the lower respiratory tract which are susceptible to the administration of such agents.</p>			

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Preparations for the application of anti-inflammatory, especially  
antiseptic agents and/or agents promoting the healing of wounds,  
to the lower respiratory tract

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The invention concerns preparations for the application of agents with anti-inflammato-  
ry, especially antiseptic and/or wound healing promoting properties to  
the lower respiratory tract. The preparations are specifically applied to trachea,  
bronchi and alveoli in the lower respiratory tracts of humans and animals.

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Furthermore, the invention concerns a method of preventing or treating infections  
by applying a pharmaceutical preparation.

15

A plurality of different antibiotic and antiseptic agents are known for the topical  
treatment of infectious maladies. A decisive disadvantage of antibiotic agents is  
that the infecting bacteria show primary resistances, and can acquire secondary  
resistances, against these agents. Further, antibiotics quite often lead to patient  
sensibilisation. The use of e.g. halogen-releasing antiseptics such as povidone  
iodine, also known as polyvidone iodine or PVP-iodine, i.e. the poly(1-vinyl-2-  
20 pyrrolidin-2-one)-iodine complex, can prevent resistances. Antiseptic agents are  
also much more rarely allergenic as compared to antibiotics.

At present, infectious diseases of the respiratory tract are treated with antibiotics.  
The application of antibiotic agents via the respiratory tract has been the subject of  
several reviews and articles with an emphasis on the lower respiratory tract.  
25 Ramsey et al., for example, describe the intermittent administration of inhaled  
tobramycin in patients with cystic fibrosis in "The New England Journal of  
Medicine", Volume 340, Number 1, 1999, p. 23-30.

The aerosolization of imipenem/cilastatin for preventing pseudomonas-induced acute lung injury has been investigated by Wiener-Kronish in "Journal of Antimicrobiol Chemotherapy" (1996) 38, p. 809-818.

- 5 Pulmonary applications of different antibiotic agents, like benzyl penicillin, tobramycin or amikacin, for the treatment of infectious diseases are described by Schreier in several recent reviews, e.g. in "Medical applications of liposomes", Papahadjopoulos and Lasic (eds.), Elsevier 1998.
- 10 However, the treatment with antibiotics leads to the complications known to the skilled person. For example, patients suffering from acute or chronic bronchitis are often treated with antibiotics in order to alleviate the symptoms. This often merely leads to resistances of the bacteria responsible for the symptoms. Many diseases of the respiratory tract are caused by viruses. Antibiotics are inefficient
- 15 in such cases, and such patients are not cured of the infections.

- 20 The use of antiseptics and/or wound-healing promoting agents for external application to humans and animals is disclosed in our earlier patent EP 0 639 373. Specifically, liposome preparations of PVP-iodine are shown therein to be topically applicable to the external parts of the eye. These preparations generally take the form of a cream, an ointment, a lotion, a gel or a drop formulation.

- 25 Liposomes are well-known drug carriers and therefore the application of medicaments in liposomal form has been subject of investigation for quite some time. An overview concerning pulmonary delivery of liposome encapsulated drugs in asthma therapy is provided by the review "Pulmonary delivery of liposomes" (H. Schreier, in "Journal of Controlled Release", 24, 1993, p.209-223). The physicochemical characterization of liposome aerosols and also their therapeutic applications to the respiratory tract are shown therein. Drugs that have

been investigated for pulmonary delivery via liposomes include, e.g. anti-cancer agents, peptides, enzymes, anti-asthmatic and anti-allergic compounds and, as mentioned above, also antibiotics. The formulation of liposome aerosols or liposome powder aerosols using, for example a dry powder inhaler has also been  
5 described by H.

Schreier in "Formulation and in vitro performance of liposome powder aerosols" (S.T.P. Pharma Sciences 4, 1994, p.38-44).

10 Although a lot of attention has been paid to liposomes as drug carriers, as can be seen from the cited documents, there appears to be no prior art relating to liposomes and other particulates as carriers of anti-inflammatory, antiseptic and/or wound-healing promoting agents for applications in the body, especially in the lower respiratory tract, including the trachea, bronchi and alveoli.

15 Some of the prior art cited above is concerned with liposome preparations. It should be understood that alternative drug carriers of a similarly particulate character exist. These drug carriers can often -and also in the context of this invention- be used instead of liposomes and include microspheres (generally comprising lipophilic polymers), nanoparticles, "Large Porous Particles" and individually coated drug substance molecules, e.g. made by using pulsed laser deposition (PLD) techniques. These PLD methods can be used to apply coatings to drug powders and to modify surface properties and release rate to a variety of drug systems.  
20

25 Where hereinafter reference is made to liposomes or particulate carriers, it is to be understood that this is to incorporate such alternative carriers, too.

It is known in the art that the administration of inhalable particles to the respiratory tract can be achieved by nebulization or aerosolization of the liposome, microsphere, Large Porous Particle, PLD or nanoparticle preparations or by dry powder inhalation of the respective preparation.

5

There appears to be a marked reluctance in the art, to apply disinfectants to interior parts of the body, except maybe in extreme cases of life-threatening septal complications.

10     Generally, antibiotic preparations appear to be preferred, even in view of their above-discussed disadvantages.

An object of the instant invention is to provide a well tolerated, easily applicable anti-inflammatory, antiseptic and/or wound-healing promoting preparation, which  
15     provides protracted release and protracted topical effect of the active agent in the lower respiratory tract.

According to the invention this object is attained in that the preparation comprises at least one anti-inflammatory, antiseptic and/or wound healing promoting agent in  
20     the form of a particulate carrier preparation, as defined in independent claim 1.

The invention further comprises a method of treating the lower respiratory tract, in humans and animals, as defined in independent claims 21 and 22.

25     The dependent claims define further advantageous embodiments of the invention.

In the context of this invention, anti-inflammatory agents are understood to include antiseptic agents, antibiotic agents, corticosteroids, and wound-healing agents, as defined below.

- 5 -

In the context of this invention, antiseptic agents are understood to include those disinfecting agents which are pharmaceutically acceptable and suitable for the treatment of the lower respiratory tract to the extent that they can be formulated in accordance with the invention.

5

More specifically, antiseptic agents include inter alia oxygen- and halogen-releasing compounds; metal compounds, e.g. silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, 10 quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

Wound-healing agents comprise agents promoting granulation and epithelialization such as dexpantenol, allantoines, azulenes, tannines, and vitamine B-type 15 compounds.

The invention is premised on the surprising fact that particulate carriers, especially liposomes, but also microspheres, nanoparticles and coated drug substance molecules, are highly suited as carriers for antiseptic agents, especially for 20 povidone iodine, and for agents promoting the healing of wounds, for application to the lower respiratory tract.

The preparations according to this invention permit protracted release of the agent or agents, and provide an extended and topical activity at the desired locus of 25 action by interaction with cell surfaces.

The invention is, another aspect, based on a further surprising and unexpected fact. It is well known in the art that the formation of new body tissues may cause problems. Thus, it is known that body tissue repair may be accompanied by the

formation of scar tissue, which can be functionally and/or cosmetically harmful, or at least undesirable. Hyperkeratosis and the uncontrolled proliferation of tissue may cause serious harm, leading to dysfunctions, and may of course also be cosmetically undesirable. After infections and inflammations, re-growing or 5 healing tissue may cause neoplasms and intergrowth. It is thus well known in the art that in the curing of diseases, proper remodelling of tissue is not only desirable, but in fact necessary.

It has now been surprisingly found that the use of anti-inflammatory agents, singly 10 or in combination with other such agents, leads to markedly less formation of undesirable body tissue in the course of tissue repair and other tissue growth processes. Thus, the formation of scar tissues is reduced, in skin but also in mucosa and in other tissues, such as muscle or inner organ tissues. Hyperkeratosis may be entirely suppressed, and intergrowth, or neoplasm formation in the curing 15 of infective diseases is also highly reduced.

One object achieved by the invention is therefore concerned with improved tissue repair in the body. The invention achieves this by the application of anti-inflammatory agents, in the form of a particulate carrier preparation as defined in 20 the independent claims.

The anti-inflammatory, antiseptic and/or wound-healing preparation can be administered to the respiratory tract by a nebulization agent loaded of the particulate carrier preparation, or by dry powder inhalation of the respective 25 preparation. For example, a liposome preparation can be made by loading liposomes with PVP iodine in a conventional procedure.

It is also possible to compact the loaded liposomes, optionally together with auxiliary materials, such as low molecular sugars, preferably lactose, to a tightly

compacted solid medicament reservoir. This medicament stock can then be abraded or micronized or treated in other ways to yield the powder in particle form. The resulting liposome preparation can be administered by inhalation of the preparation in the form of a powder aerosol, as, for example, described in "Acute Effects of Liposome Aerosol Inhalation on Pulmonary Function in Healthy Human Volunteers" (Thomas et al., Preliminary report, Volume 99, 1991, p. 1268-1270). The pressures for preparing the tightly compacted solid medicament stock are preferably in the range of from 50-500 MPa. Such medicament stock is described in WO 94/14490 and a device for administration is disclosed in WO 93/24165.

10

The nature or constitution of the liposomes is generally not critical. The liposome preparation as, for example, described in EP 0 639 373 can be administered by inhalation as an aerosol. The disclosure of EP 0 639 373 is incorporated by reference.

15

The preparations according to this invention apparently do not only contain the active agent, like povidone iodine, encapsulated in the particulate carrier, especially in liposomes. It seems that there is also some amount of agent which is not contained inside the carrier. The preparations according to the invention often show a marked initial effect which is observed in addition to the slower, protracted release of the active agent from the carrier. This effect is especially observed where the carrier comprises liposomes. Without wishing to be bound to any theoretical explanation, it is presently assumed that in addition to active agent encapsulated inside the liposomes, some active agent is present outside of the liposomes, and probably loosely bound to the outer surfaces of the liposomes. This could be due to association of active agent molecules with the liposomal membrane, or it could be due to active agent molecules forming a layer on the liposomal surface, which layer partly or even fully coats the liposome externally. The type and amount of this initial agent effect can e.g. be influenced by choice

of the concentration parameters.

The amphiphilic substances generally known in prior art to form liposome membranes can be employed in the context of the invention as long as they are pharmaceutically acceptable for the intended application. Presently, liposome forming systems comprising lecithin are preferred. Such systems can comprise hydrogenated soy bean lecithin besides cholesterol and disodium succinate-hexahydrate; it is presently specifically preferred to use hydrogenated soy bean lecithin as the sole membrane-forming agent.

10

The known prior art methods for forming liposome structures are described in the documents cited above and can generally be used in the context of the invention. Broadly, these methods comprise mechanical agitation of a suitable mixture containing the membrane forming substance and water or an aqueous solution. 15 Filtration through suitable membranes is preferred in forming a substantially uniform liposome size.

The average size of the liposomes according to this invention can vary over a broad range, generally from about 1 to about 50  $\mu\text{m}$ , preferably in the range of 1 20 and 30  $\mu\text{m}$  diameter. For solutions, smaller average diameters, e.g. diameters of about 100 nm, may be more suitable.

The liposomes according to this invention have a substantially uniform size in the range between about 20 and 30  $\mu\text{m}$  diameter for application to the trachea, in the 25 range between about 10 and 20  $\mu\text{m}$  diameter for application to the bronchi and between about 1 and 6  $\mu\text{m}$ , especially between 2 and 5  $\mu\text{m}$ , diameter for application to the alveoli.

Where alternative particulate carriers are used, they are generally prepared as known in the art. Thus, microspheres which are used to deliver a very wide range of therapeutic or cosmetic agents, are made as described for example in WO 95/15118.

5

Nanoparticles may in some cases be used, provided that they can be loaded with a sufficient amount of active agent and can be administered to the lower respiratory tract according to this invention. They can be prepared according to the methods known in the art, as e.g. described by Heyder (GSF München) in "Drugs delivered to the lung", Abstracts IV, Hilton Head Island Conference, May 1998.

10 Methods using a pulse laser deposition (PLD) apparatus and a polymeric target to apply coatings to drug powders in a short non-aqueous process are also suitable for the formation of particulate preparations according to this invention. These 15 have e.g. been described by Talton et al., "Novel Coating Method for Improved Dry Delivery", Univ. of Florida UF 1887 (1998).

A further suitable delivery system employs Large Porous Particles as disclosed by David A. Edwards et al. in "Large Porous Particles for Pulmonary Drug Delivery" 20 (Science, 20. June 1997, Vol. 276, p. 1868-1871). The average size of Large Porous Particles according to this invention can e.g. be in the range of between about 5 and 20  $\mu\text{m}$  diameter for application to the alveoli.

25 Preferred anti-inflammatory agents comprise antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents, as single substances or in combination with each other.

Preferred antiseptic agents comprise the well-known pharmaceutical substances providing fast effect, a broad range of activity, low systemic toxicity and good

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tissue compatibility. They can e.g. be selected from the group comprising metal compounds, phenolic compounds, detergents, iodine and iodine complexes. A specifically preferred antiseptic agent is povidone iodine.

- 5 Preferred agents promoting the healing of wounds comprise substances which have been described in the literature for such application. Preferred such agents include substances known to promote epithelisation. These include vitamins, specifically from the vitamin B group, allantoin, some azulenes etc.
  - 10 Some presently highly preferred embodiments of the invention comprise anti-inflammatory agents or combinations of such agents which show beneficial effects in tissue repair, especially with respect to functional and cosmetic tissue remodelling. In these embodiments, the active agent is often an antiseptic, such as PVP-iodine, or an antibiotic.
  - 15 In preferred embodiments, the invention's preparations containing anti-inflammatory, especially antiseptic and/or wound-healing promoting agents can comprise further agents such as anaesthetic agents. Inventive preparations can also contain customary further agents, including adjuvants and additives,
  - 20 antioxidants, conserving agents or consistency-forming agents such as viscosity adjusting additives, emulgators etc.
- Generally, the concentrations in the preparation, particle sizes, active agent loadings etc. will be selected for such alternative carriers to correspond basically to the parameters discussed herein with respect to liposome preparations. Selecting and providing such parameter based inter alia on straightforward experimentation, is well within the skill of an ordinary worker experienced in this art.

- A presently highly preferred use of the inventive liposome preparations is in the treatment of infections of the lower respiratory tract, including trachea, bronchi and alveoli, especially when the liposome preparations contain povidone iodine.
- Also in this indication, the inventive antiseptic preparations, especially those containing PVP iodine, have the great advantage of not causing resistances and lead to much less allergic reactions, while permitting a very cost-efficient therapy with a broad spectrum of effect. A povidone iodine liposome preparation according to this invention is e.g. effective against viruses. Further, a liposome preparation of a microbicidal agent such as povidone iodine provides protracted release of the agent from liposomes delivering the agent to the pulmonary regions, for example to the alveolar regions of the lung. This leads to extended effect of the antimicrobial substance, and thus less frequent application, as compared with the customary antiseptic solution preparations.
- The present invention is also useful in the treatment of infectious diseases or for alleviation of diseases such as HIV infections which are accompanied by opportunistic infections. Also patients having a suppressed immune system, for example, after organ transplants, can be treated according to the invention. In particular, acute and chronical bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria, tuberculosis can be treated with the povidone iodine preparation according to the invention.
- Further highly preferred use is in tissue repair, especially in functional and cosmetic tissue remodelling.
- Preparations according to this invention can take a variety of forms, which are suitable for administration via the lower respiratory tract, including pharmaceutically acceptable solid or liquid formulations, which are suitable for the generation of inhalable particles. Preparations according to this invention can be

therefore in the form of (powder) aerosol or in the form of a compacted solid medicament reservoir, preferably a ring tablet, more preferably a gelatine capsule, a powder, a spray, an emulsion, a dispersion, a suspension or even a solution containing the carrier and agent or agents.

5

Generally, the amount of active agents in an inventive preparation will be determined by the desired effect, on the one hand, and the carrying capacity of the carrier preparation for the agent, on the other hand.

- 10 For inventive preparations with large amounts of active agents or high dosages of active agent, nebulized preparations or aerosols are preferred to powders or powder aerosols. Broadly, the amount of active agent in an inventive carrier preparation can range in concentrations between the lower limit of effectiveness of the agent and the maximum loading of the agent in the respective carrier  
15 preparation.

- More specifically, for an antiseptic agent, such as povidone iodine, a solution or dispersion in an inventive carrier preparation, especially where the carrier is a liposome preparation, can contain between 0.1 and 10 g of agent in 100 g of  
20 preparation. Such a preparation will then typically contain between 1 and 5 g of liposome membrane-forming substance, especially lecithin, per 100 g of preparation.

- An inventive aerosol or spray preparation will often comprise up to 50 mg, but  
25 could comprise up to and above 100 mg of liposomal active agent formulation and can, for example, be administered by 5 spray doses, each containing 20 mg of liposomal active agent formulation.

The preparation will typically comprise at least 10 % wt of active agent such as PVP-iodine in the loaded liposomes (or alternative carrier particles), but may comprise up to 50 wt.-% or even more of active agent. Where the active agent is PVP-iodine, the amount of available iodine will generally be about 10 wt.-%  
5 (based on PVP-iodine).

More specific formulations are notable from the embodiment examples.

The features and advantages of this invention will become notable in more detail  
10 from the ensuing description of preferred embodiments. In these embodiments, which include a best mode, povidone iodine is exemplified as an antiseptic agent and liposomes are chosen as the carrier. This should, however, not be construed as a restriction of this invention to antiseptic agents or, among antiseptic agents, to povidone iodine, and/or to liposomes as the carrier, although such preparations are  
15 specifically preferred.

One preferred method for producing the invention's liposomes can generally be described as follows:

20 The lipid membrane-forming components, e.g. lecithin, are dissolved in a suitable solvent such as chloroform or a 2:1 mixture of methanol and chloroform and are filtered under sterile conditions. Then, a lipid film is produced on a sterile high surface substrate, such as glass beads, by controlled evaporation of the solvent. In some cases, it can be quite sufficient to form the film on the inner surface of the  
25 vessel used in evaporating the solvent, without using a specific substrate to increase the surface.

An aqueous system is prepared from electrolyte components and the (one or more) active agents to be incorporated in the liposome preparation. Such an aqueous

system can e.g. comprise 10 mmol/l sodium hydrogen phosphate and 0.9 % sodium chloride, at pH 7.4; the aqueous system will further comprise at least the desired amount of the active agent, which in the embodiment examples is povidone iodine. Often, the aqueous system will comprise an excess amount of  
5 agent or agents.

The liposomes are generally formed by agitating said aqueous system in the presence of said film formed by the lipid components. At this stage, further additives can be added to improve liposome formation; e.g. sodium cholate can be  
10 added. Liposome formation can also be influenced by mechanical action such as pressure filtration through e.g. polycarbonate membranes, or centrifuging. Generally, the raw liposome dispersion will be washed, e.g. with electrolyte solution as used in preparing the above-described solution of the active agent.

15 When liposomes with the required size distribution have been obtained and washed, they can be redispersed in an electrolyte solution as already described, often also comprising sugars such as saccharose or a suitable sugar substitute. The dispersion can be freeze-dried, and it can be lyophilised. It can, prior to use, be reconstituted by addition of water and suitable mechanical agitation at the  
20 transition temperature of the lipid component, which for hydrogenated soy bean lecithin is e.g. 55°C.

In the following Examples, hydrogenated soy bean lecithin (EPIKURON (TM) 200 SH obtainable from Lukas Meyer, Germany or PHOSPOLIPON (TM) 90 H  
25 obtainable from Nattermann Phospholipid GmbH, Germany) was used. However, other pharmaceutically acceptable liposome membrane-forming substances can be used instead, and the person skilled in the art will find it easy to select suitable alternative liposome forming systems from what is described in prior art.

Embodiment Example I

In a 1000 ml glass flask, provided with glass beads for increased surface, 51.9 mg cholesterol and 213 mg hydrogenated soy bean lecithin were dissolved in a sufficient amount of a mixture of methanol and chloroform in a 2:1 ratio. The solvent was then evaporated under vacuum until a film was formed on the inner surface of the flask and on the glass beads.

2.4 g PVP iodine (containing about 10 % available iodine) were separately dissolved in 12 ml water.

Again in a separate vessel, 8.77 g sodium chloride and 1.78 g Na<sub>2</sub>HPO<sub>4</sub>·2H<sub>2</sub>O were dissolved in 400 ml water. Further water was added up to a total volume of 980 ml, and then, approximately 12 ml 1N hydrochloric acid were added to adjust pH to 7.4. This solution was then topped up with water to exactly 1000 ml.

In a fourth vessel, 900 mg saccharose and 57 mg disodium succinate were dissolved in 12 ml water.

The PVP iodine solution was then added to the lipid film in the flask and the mixture was shaken until the film dissolved. The resulting liposome formulation was separated from the hydrated lipids in the flask. The product was centrifuged and the supernatant liquid was discarded. The saccharose solution was added ad 12 ml and the product was again centrifuged. Afterwards the supernatant liquid was again discarded. At this stage, a further washing step, using the saccharose solution or the sodium chloride buffer solution could be carried out.

After the last centrifugation step and discarding of the supernatant, 12 ml sodium chloride buffer solution was added, and the liposomes were homogenously

distributed therein. The product was then distributed into vials each containing 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step.

After the freeze-drying, each vial comprised about 40 mg solids.

5

The method of Embodiment Example I has a minor disadvantage in that the PVP iodine solution used, due to the high percentage of solids, is rather viscous and thus more difficult to handle.

10      Embodiment Example II

In a 2000 ml flask provided with glass beads to increase surface, 173 mg hydrogenated soy bean lecithin and 90 mg disodium succinate were dissolved in approximately 60 ml of a methanol/chloroform mix in a 2:1 ratio. The solvent 15 was removed under vacuum until a film was formed.

4 g PVP iodine (10 % available iodine) were dissolved in 40 ml of the sodium chloride buffer solution described in Embodiment Example I, and were added to the lipid film in the flask. The flask was then shaken until the film dissolved and 20 liposomes were formed.

The product was centrifuged and the supernatant liquid was discarded.

To the thus produced liposome pellet, further 40 ml sodium chloride buffer 25 solution was added, and the centrifuging step was repeated. The supernatant was again discarded. At this stage, the washing step could be repeated where necessary.

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After the final centrifuging and decanting step, 40 ml sodium chloride buffer solution was again added to the precipitated liposomes. The homogenous dispersion was then distributed into vials, each vial containing about 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step.

5 This produced approximately 200 mg freeze-dried solids per vial.

Like that of Embodiment Example I, the above-described method uses a hydrating step after film formation in the presence of organic solvents and aims at inclusion rates of 5 to 15 %. These methods generally produce rather large and often multi-lamellar liposomes.

10 The above-described methods can be modified by a high pressure filtering step through a suitable membrane such as a polycarbonate membrane after the raw liposomes have been formed or after any of the subsequent washing steps or directly by using high pressure homogenisation. This produces much smaller, 15 unilamellar liposomes at increased amounts of encapsulated agent.

Instead of high pressure homogenisation, other prior art methods known to provide small uniform sized liposomes can be employed.

20 Embodiment Example III

A gelatine capsule, which is suitable for the generation of inhalable particles, was prepared from 20 g of povidone iodine liposomes containing leophilised (?????) material according to the above-mentioned general preparation method and 20 mg lactose by applying pressures of up to 500 MPa. From the obtained hard capsule a powder or powder aerosol was generated by abrading methods using a powder inhaler (Orbital-Inhaler by Brin Tech International Ltd.

It is also possible to prepare embodiments similar to those described above, which comprise an agent capable of promoting the healing of wounds insteads of, and not in addition to, the antiseptic agent, such as e.g. povidone iodine disclosed in the above embodiment examples. Presently, it is however preferred to use a  
5 wound healing promoting agent (if at all) in addition to an antiseptic agent.

For application of the inventive preparations to a patient, known systems can be used, such as inhalers, powder inhalers, two-chamber gas pressure packs, aerosol spray dispensers, nebulizers, compressors, etc.

10

#### Embodiment Example IV

Liposomal preparations were aerosolized via an air-driven nebulizer. The output and aerosol characteristics of liposomes with the nebulizer have been previously  
15 described. The resulting droplets had a mass medium aerodynamic diameter of about 2.4 µm and are therefore suitable for deposition in the alveolar region.

Using inventive preparations efficiency tests were then carried out, as follows:

20 Test I

This was an in-vitro-test of the bactericidal effect provided by an inventive povidone iodine liposome preparation. The test was based on the quantitative suspension test as described in "Richtlinien der Deutschen Gesellschaft für Hygiene und Mikrobiologie", 1989. In this test, the bactericidal agent is used to  
25 kill staphylococcus aureus (ATCC 29213), a major problem in hospital hygiene.

The liposome preparation used was that of Embodiment Example I. At different contact times between 1 und 120 minutes, the minimum concentration of the preparation in water was determined which was capable of killing the

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staphilococci.

The results are shown in Table 1.

5

TABLE I

	<u>Contact Time (Minutes)</u>	<u>Bactericidal Concentration</u>
	1, 2, 3, 4	≥ 0.060 %
	5, 30, 60	≥ 0.015 %
10	120	≥ 0.007 %

The results show that at short contact times (between 1 and 4 minutes) the bactericidal concentration is as low as 0.06 % and that at long contact times (120 minutes) the bactericidal concentration can be as low as 0.007 %.

15

Test II

The virucidal and chlamydicidal activity of liposomal PVP-iodine has been studied, in cell cultures, by Wutzler et al., 9th European Congress for Clinic Microbiology and Infection Diseases, Berlin, March 1999. In cell cultures, 20 liposomal PVP-iodine is highly effective against herpes simplex virus type 1 and adenovirus tpye 8, while the long-term cytotoxicity experiments indicated that the liposomal form is better tolerated than aqueous PVP-iodine by the majority of cell lines tested. PVP-iodine in liposomal form is not genotoxic.

25

Test III

A 3% PVP-iodine hydrogel liposomal preparation was compared with a 3% PVP-iodine ointment, where the active agent was not in liposomal form. The agent

- 20 -

was applied to standardized in vitro cultures of rat skin and peritoneal explants, as a screening for tissue compatibility of skin and wound antiinfectives.

The growth rate of the cultured explants was studied after 30 minutes exposure  
5 and incubation with a test substance.

Again, the substantially better toleration of the liposomal preparation was clearly shown in the results, in terms of peritoneum growth rate and skin growth rate.

10 With the ointment, the peritoneum growth rate reached 85%, and the skin growth rate reached 90%; with the liposomal hydrogel formulation, the peritoneum growth rate was 96%, and the skin growth rate was 108%; these values are to be compared with 100% values in a control test using Ringer's solution as the agent.

15

Claims

1. A process for the manufacture of a pharmaceutical preparation for the application of antiseptic agents and/or agents which promote the healing of 5 wounds to the lower respiratory tract, characterised in that the preparation contains at least one of said agents combined with a particulate carrier.

2. The process of claim 1, 10 characterised in that said particulate carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation or a laser-pulse polymer coated molecule preparation.

3. The process according to claim 1 or 2, 15 characterised in that at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

4. The process of any one of claims 1 to 3, 20 characterised in that the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines,

hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

5. The process according to claim 4,

characterised in that the antiseptic agent is selected from the group comprising metal compounds such as mercury compounds, phenol derivatives such as thymol, eugenol and hexachlorophene, iodine and iodine complexes.

6. The process according to claim 5,

10 characterised in that the antiseptic agent is povidone iodine.

7. The process according to any one of claims 1 to 6,

characterised in that the wound-healing promoting agent is selected from agents promoting granulation and epithelization such as dexpantenol, allantoines, 15 azulenes, tannines, compounds from the vitamin B series, or similarly acting agents.

8. The process according to any one of the preceding claims,

characterised in that the preparation contains at least one antiseptic and at least 20 one wound-healing promoting agent.

9. The process according to any one of the preceding claims,  
characterised in that the carrier particles, especially liposomes, have a substantially  
uniform size in the range between about 1 and about 50  $\mu\text{m}$ , preferably in the  
range between about 1 and about 30  $\mu\text{m}$ .

5

10. The process according to claim 9,  
characterised in that the carrier particles, especially liposomes, have a substantially  
uniform size in the range between about 20 and 30  $\mu\text{m}$  diameter for application to  
the trachea, in the range between about 10 and 20  $\mu\text{m}$  diameter for application to  
the bronchi and between about 1 and 6  $\mu\text{m}$ , especially between 2 and 5  $\mu\text{m}$ ,  
diameter for application to the alveoli.

11. The process according to any one of the preceding claims,  
characterised in that the carrier, especially liposome, preparation releases the agent  
15 over an extended time period, preferably an extended time period of several hours  
duration.

12. The process according to claim 11,  
characterised in that the carrier, especially liposome, preparation releases the agent  
20 at approximately the same release rate over the release time period.

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13. The process according to any one of the preceding claims,  
characterised in that the preparation additionally comprises at least one  
anaesthetically active agent.

5 14. The process according to any one of the preceding claims,  
characterised in that the preparation contains additives and adjuvants such as  
conserving agents, antioxidants and consistency-forming additives.

10 15. The process according to any one of claims 1 to 14, the preparation  
being in a suitable form for administration via the lower respiratory tract  
comprising the active-agent loaded carrier, especially in the form of liposomes,  
preferably in the form of an aerosol, especially in the form of a powder aerosol.

15 16. The process according to any one of claims 1 to 14, the preparation  
being in the form of a compacted solid medicament reservoir, preferably a ring-  
tablet, more preferably a gelatin capsule, a powder, a spray, an emulsion, a  
dispersion, a suspension or a solution containing the carrier and agent or agents in  
a pharmaceutically acceptable solid or liquid formulation, which is suitable for the  
generation of inhalable particles.

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17. The process according to any one of the preceding claims, the preparation being in a suitable form for administration via the lower respiratory tract, which comprises:

- a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and
  - 5 b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,
- wherein the liposomes are of substantially uniform size between about 1  
10 and about 50  $\mu\text{m}$ , and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical formulation.

18. The process according to claim 17,  
characterised in that the liposomes are of substantially uniform size, in the range  
15 between about 20 and 30  $\mu\text{m}$  diameter for application to the trachea, in the range between about 10 and 20  $\mu\text{m}$  diameter for application to the bronchi and between about 1 and 6  $\mu\text{m}$  diameter, preferably between about 2 and 5  $\mu\text{m}$  diameter, for application to the alveoli.

20 19. The process according to any one of claims 1 to 18, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections

or a suppressed immune system.

20. The process according to any one of claims 1 to 18, wherein the preparation is suited for the treatment of acute and chronic bronchitis, pneumonia,  
5 bronchiectasia, cystic fibrosis, diphtheria and/or tuberculosis.

21. The process according to any one of claims 1 to 20, wherein the preparation is suited for functional and cosmetic tissue remodelling and repair treatments.

10

22. A method of preventing or treating infections of the human or animal lower respiratory tract, by applying, to said tract, a pharmaceutical preparation comprising at least one antiseptic agent and/or wound-healing promoting agent, said agent being combined with a particulate carrier in said  
15 preparation.

23. A method of functional and cosmetic tissue remodelling and repair in the human or animal lower respiratory tract, by applying, to said tract, a pharmaceutical preparation comprising at least one anti-inflammatory especially  
20 antiseptic and/or wound-healing promoting agent combined with a particular carrier.

24. The method of claim 22 or 23, wherein said carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation, or a laser-pulse polymer coated molecule preparation.

5

25. The method of claim 22 or 23, wherein at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.

10

26. The method of claim 23, wherein the anti-inflammatory agent is selected from antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents.

15

27. The method of claim 22 or 23, wherein the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

20

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28. The method of claim 22 or 23, wherein the antiseptic agent is selected from the group comprising metal compounds such as mercury compounds phenol derivatives such as thymol, eugenol and hexachlorophene, iodine and iodine complexes.

5

29. The method of claim 22 or 23, wherein the antiseptic agent is povidone iodine.

30. The method of claim 22 or 23, wherein the wound-healing 10 promoting agent is selected from agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, compounds from the vitamin B series or similarly acting agents.

31. The method of claim 22 or 23, wherein the preparation contains at 15 least one antiseptic and at least one wound-healing promoting agent.

32. The method of claim 22 or 23, wherein the carrier particles, especially liposomes, have a substantially uniform size in the range between about 1 and about 50  $\mu\text{m}$ , preferably in the range between about 1 and about 30  $\mu\text{m}$ .

20

33. The method of claim 32, wherein the carrier particles, especially liposomes, have substantially uniform size in the range between about 20 and 30  $\mu\text{m}$  diameter for application to the trachea, in the range between about 10 and 20  $\mu\text{m}$  diameter for application to the bronchi and between about 1 and 6  $\mu\text{m}$  diameter, especially between 2 and 5  $\mu\text{m}$ , for application to the alveoli.

5  
34. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

10

35. The method of claim 22 or 23, wherein the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

15  
36. The method of claim 22 or 23, wherein the preparation additionally comprises at least one anaesthetically active agent.

20  
37. The method of claim 22 or 23, wherein the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

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38. The method of claim 22 or 23, the preparation being in a suitable form for administration via the lower respiratory tract comprising the active-agent loaded carrier, especially in the form of liposomes, preferably in the form of an aerosol, especially in the form of a powder aerosol.

5

39. The method of claim 22 or 23, the preparation being in the form of a compacted solid medicament reservoir, preferably a ring-tablet, more preferably a gelatine capsule, a powder, a spray, an emulsion, a dispersion, a suspension or a solution containing the carrier and agent or agents in a pharmaceutically acceptable solid or liquid formulation, which is suitable for the generation of inhalable particles.

10 40. The method of claim 22 or 23, the preparation being in a suitable form for administration via the lower respiratory tract, which comprises:

15 a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and

b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

20 wherein the liposomes are of substantially uniform size between about 1 and about 50 µm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical formulation.

41. The method of claim 22 or 23, wherein the liposomes are of substantially uniform size, between about 20 and 30  $\mu\text{m}$  diameter for application to the trachea, between about 10 and 20  $\mu\text{m}$  diameter for application to the bronchi and between about 1 and 6  $\mu\text{m}$ , preferably between about 2 and 5  $\mu\text{m}$  diameter, for application to the alveoli.

42. The method of claim 22 or 23, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections or a suppressed immune system.

43. The method of claim 22 or 23, wherein the preparation is suited for the treatment of acute and chronic bronchitis, pneumonia, bronchiectasia, cystic fibrosis, diphtheria and/or tuberculosis.

# INTERNATIONAL SEARCH REPORT

Internat'l Application No  
PCT/EP 99/03681

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 639 373 A (EUROCELTIQUE) 22 February 1995 (1995-02-22) claims 1-18 ---	1-43
A	EP 0 613 685 A (GONZALEZ ENSENAT, PEDRO, ET AL.) 7 September 1994 (1994-09-07) claim 1 column 4, line 19 - line 26 ---	1-43
A	EP 0 509 338 A (MERZ & CO.) 21 October 1992 (1992-10-21) claims 1,9 example 7 ---	1-43
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

25 October 1999

Date of mailing of the International search report

09/11/1999

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## INTERNATIONAL SEARCH REPORT

Internat'l Application No  
PCT/EP 99/03681

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 (1992-09-07) Columbus, Ohio, US; abstract no. 97244, GILBERT, BRIAN E. ET AL: "Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice" XP002119931 abstract &amp; ANTIMICROB. AGENTS CHEMOTHER. (1992), 36(7), 1466-71 ,1992, -----</p>	1-3, 9-12, 14-16, 18-26, 32-35, 37-39, 41-43

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/03681

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 22-43 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Internat'l Application No
PCT/EP 99/03681

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 639373	A 22-02-1995	DE AT DE DE ES GR JP SI US	9312509 U 173917 T 69414936 D 69414936 T 2124822 T 3029436 T 7145081 A 639373 T 5863556 A	28-10-1993 15-12-1998 14-01-1999 12-08-1999 16-02-1999 28-05-1999 06-06-1995 30-04-1999 26-01-1999
EP 613685	A 07-09-1994	DE AT DE ES	4306475 A 173158 T 59407247 D 2124328 T	08-09-1994 15-11-1998 17-12-1998 01-02-1999
EP 509338	A 21-10-1992	DE AT CA DE DK ES GR JP US	4111982 A 126430 T 2065579 A 59203259 D 509338 T 2077904 T 3017147 T 7048247 A 5498420 A	15-10-1992 15-09-1995 13-10-1992 21-09-1995 18-09-1995 01-12-1995 30-11-1995 21-02-1995 12-03-1996